958-93 Prevention of Mental Stress-induced Wall Motion Abnormalities by Nifedipine GITS and Atenolol Therapy

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Previous investigators have demonstrated that mental stress can induce myocardial ischemia in selected patients with coronary disease manifested by new wall motion abnormalities on radionuclide ventriculography. It is unknown whether such ischemia is due to coronary vasoconstriction or to increased myocardial O_2 demand. We studied the effect of nifedipine GITS and atenolol as single-agent therapy on mental stress-induced ischemia in a double-blind, placebo-controlled, three-way crossover trial in 16 patients with stable angina. Each patient received maximally tolerated doses of nifedipine (mean daily dose: 88 mg), atenolol (mean daily dose: 91 mg) or placebo during each of 3 4-week treatment phases. At the end of each phase, patients underwent a mental stress procedure (Stroop color word test, mental arithmetic, and stress interview) with skin conductance monitored to gauge physiologic arousal. Left ventricular wall motion was graded in each of 5 regions using a scale from 3 (normal) to −1 (dyskinesis), and by regional ejection fraction. The segment with the largest deterioration in wall motion during placebo therapy was determined, and the effects of nifedipine and atenolol on this segment were compared. *Results:* Mental stress caused a significant increase in skin conductance levels, with peak values similar on each therapy. Therapy with either nifedipine or atenolol prevented a deterioration in wall motion score (−0.6 for placebo; 0.0 for nifedipine, 0.0 for atenolol, each $p < 0.01$ vs. placebo), while only nifedipine prevented a significant decrease in regional ejection fraction (−13.0% on placebo; −5.6% for atenolol, $p = 0.08$ vs. placebo; −1.9% on nifedipine, $p = 0.01$ vs placebo, $p = 0.4$ vs. atenolol). The rate pressure product (heart rate × systolic blood pressure, RPP) at peak mental stress (i.e., peak myocardial O_2 demand) was 15,792 on placebo, and was reduced only by atenolol (12,287, $p = 0.001$), but not by nifedipine (15,185, p = NS). *Conclusion:* Both nifedipine GITS and atenolol are effective at preventing mental stress-induced ischemic wall motion abnormalities, although the mechanisms may be different. Nifedipine improved regional wall motion without reducing RPP, and thus may have prevented mental stress-induced coronary vasoconstriction. Atenolol improved regional wall motion and reduced RPP, and thus may have been effective by reducing myocardial O_2 demand.

958-94 Neurohormonal and Hemodynamic Effects of SDZ WAG 994 a Novel Selective A_1 Adenosine-receptor Agonist in Patients with Heart Failure

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Effects of stable, selective A_1 adenosine receptor agonist (N^6-cyclohexyl-2'-0-methyladenosine) SDZ WAG 994 were investigated in a randomized, double-blind, placebo-controlled, parallel group, multicenter study. After baseline hemodynamic and neurohormone data were obtained in 50 patients (mean age 56 years) with left ventricular dysfunction (mean EF 30%), who were NYHA Class I (32%) or II (68%), they received either 1, 2 or 5 mg of SDZ WAG 994 or placebo orally. Hemodynamic data were collected every 30 minutes for 4 hours and then every 2 hours for 20 hours. Neurohormones and plasma drug concentration were measured 2 hours after dosing.

The active drug was clinically well tolerated as there were no significant differences comparing adverse events reported with placebo and the 3 active drug doses. No important effects were seen on systolic, right atrial, pulmonary artery or pulmonary artery wedge pressures, cardiac index, or heart rate. The PR interval increased slightly with the 5 mg dose (176 to 193 msec at 2 hrs). Atrial natriuretic peptide (ANP) levels increased significantly (216 ± 137 to 407 ± 146 pg/mL, $p < 0.01$) with the 5 mg dose and increases of lesser magnitude occurred with 1 and 2 mg doses. Interestingly, plasma norepinephrine also increased with the 5 mg dose (477 ± 243 to 618 ± 237 pg/mL, $p < 0.01$). No significant changes occurred in plasma renin activity or epinephrine levels.

In summary, selective A_1 adenosine receptor agonism, evidenced by an increase in PR interval and plasma ANP, was safely achieved for several hours in patients with LV dysfunction. Significant neurohormonal effects were observed with no important hemodynamic changes. Both A_1 adenosine agonism and ANP have been shown to attenuate hypoxic cell damage and vasoconstriction and this agent could have clinical utility in ischemic heart disease.

958-95 Long-term Effects of Amlodipine and Isosorbiddinitrate on Exercise-induced and Ambulatory Ischaemia in Patients with Stable Angina Pectoris

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Once-daily administration of 10 mg amlodipine has been compared with two daily doses of 40 mg sustained-release isosorbiddinitrate (ISDN) in 59 patients with stable angina, using a randomized, double-blind, double-placebo, crossover study design. Nine patients dropped out due to side effects (3 during amlodipine and 6 during ISDN therapy), and one patient was excluded for technical reasons.

A maximal symptom limited supine bicycle tolerance test and a 48 h ambulatory ECG monitoring were performed at the end of each 5 week period of therapy. During exercise, exercise time, time to onset of angina, and time to onset of ischaemia, i.e., 1 mm ST segment depression were measured. During ambulatory monitoring, number of anginal episodes and duration per hour of ST deviation were assessed.

Amlodipine significantly prolonged time to angina (320 ± 155 vs 304 ± 126 sec; $p < 0.05$) and time to ischaemia (292 ± 153 vs 232 ± 126 sec; $p < 0.001$), when compared with ISDN, while exercise time was similar for both treatments. Furthermore, amlodipine reduced anginal episodes (1.2 ± 1.6 vs 2.4 ± 3.0 attacks/48 h; $p < 0.001$), whereas, no difference was found between amlodipine and ISDN in duration of ST deviation during ambulatory monitoring.

In conclusions, addressing the long-term treatment of patients with stable angina pectoris, once-daily dosing of amlodipine appears to be more effective than ISDN, as determined by its anti-anginal and anti-ischaemic effects during exercise tolerance testing and ambulatory ECG monitoring.

958-96 Enalapril Does not Affect Ischemia During Short-term Treatment in Stable Angina Pectoris Irrespective of Its Effect on Blood Pressure

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Whereas ACE inhibition acutely reduces myocardial ischemia (MI) through neuroendocrine modulation and, after long-term treatment (1 year), affects ischemic events in LV dysfunction, the short-term antiischemic properties in chronic, stable anginal patients and normal LV function are debated. As a pro-ischemic effect may be explained by lowering coronary artery perfusion pressure, the effects of enalapril (E) 10 mg b.i.d. on ischemia in relation to blood pressure (BP), and placebo b.i.d. were compared in 27 patients with chronic exercise-induced angina pectoris in a double-blind cross-over trial with 2 treatment periods of 2 weeks each. Exercise performance was assessed using treadmill exercise tests. No period or treatment sequence effects were observed for BP, heart rate and exercise performance. After treatment with E, resting systolic and diastolic BP were 7% and 6%, respectively, lower compared to placebo. During maximal exercise, systolic BP and rate-pressure product (RPP) were similar during both treatments, whereas diastolic BP was 6% less with E. Maximal workload was comparable after both treatment periods. No differences between treatment were seen with regard to exercise duration, time to angina, maximal ST-depression (0.2 mV in both groups) and time to 0.1 mV ST-depression. When patients were divided into 2 groups according to BP response on an initial dose of 10 mg E, 11 pts ≥ 20 mmHg and 16 pts < 16 mmHg, still no differences during exercise were found. Thus, in stable chronic exercise-induced angina, short-term E does not decrease myocardial ischemia, irrespective of first-dose BP response. Also, no pro-ischemic effects as a result of lowering coronary artery perfusion pressure were observed.

958-97 Analysis of Heart Rate Variability may Predict Efficacy of Metoprolol in the Treatment of Myocardial Ischemia During Daily Life

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The autonomic nervous system plays an important role in the occurrence of symptomatic and silent myocardial ischemia (MI) during daily life. Analysis of heart rate variability (HRV) is a non-invasive tool which provides information on autonomic control. We investigated if analysis of HRV can be used to predict the efficacy of drug treatment of MI in a double-blind, cross-over study. Twenty eight patients with stable angina pectoris, proven coronary artery disease and MI during Holter monitoring received metoprolol controlled release 200 mg once daily and diltiazem 60 mg 4 times daily. After a placebo phase and after each treatment period, 72 hour Holter recordings were performed for analysis of HRV and MI. HRV analysis included standard deviation